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Long-Term Controlled-Release Oxycodone and Pregabalin in the Treatment of Non-Cancer Pain: An Observational Study

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Key Words

Non-cancer pain · Oxycodone · Pregabalin · Combination therapy · Long-term study

Abstract

Aims: This study evaluates the efficacy and tolerability of long-term controlled-release (CR) oxycodone + pregabalin in patients with non-cancer pain, in a real-life setting. ***Methods:*** Patients (n = 1,051) with chronic uncontrolled non-cancer pain received CR oxycodone + pregabalin for 1 year. Pain intensity was rated on an 11-point numerical rating scale (NRS) at months 1, 2, 4, 6, 9 and 12. ***Results:*** Throughout the study period, the NRS score decreased significantly (baseline: 7.02 ± 1.26; 12 months: 1.45 ± 0.92; p = 0.00001). Following an initial increase in the mean daily doses of CR oxycodone (starting dose: 12.5 ± 8.4 mg) and pregabalin (starting dose: 121.7 ± 97.2 mg), dose reductions were seen for both drugs with the trend particularly evident for CR oxycodone. 23% of patients withdrew from the study, mainly due to adverse events (67.9% of withdrawn subjects). However, 19.7% of withdrawn patients were removed from the study due to complete relief from chronic pain. The combination was generally well tolerated and there were no reports of addiction. ***Conclusion:*** The combination of CR oxycodone + pregabalin could represent a valuable long-term therapeutic addition to existing pharmacological options for the treatment of non-cancer pain.

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Introduction

Different molecular mechanisms involving peripheral and central sensitization sustain chronic pain [1]. However, most of these mechanisms are shared among the various forms of this condition [1]. Therefore, drugs specifically targeted for the treatment of neuropathic pain are effective in relieving nociceptive inflammatory pain and vice versa [1]. In particular, it has been suggested that the molecular mechanisms of sensitization that occur in peripheral nociceptors and the dorsal horns of the spinal cord could represent promising targets for context-dependent drugs, i.e. molecules able to discriminate between 'normal' and 'pathological' pain transmission. Among these drugs, pregabalin and gabapentin bind to the $\alpha_2\delta$-subunit of voltage-sensitive Ca^{2+} channels, thus inhibiting the enhanced release of pain transmitters at the synapses and limiting the severity of chronic pain [1]. Pregabalin in particular has been extensively evaluated in a number of clinical experiences and currently represents one of the recommended first-line treatments for non-cancer pain [2–4].

However, a considerable proportion of patients do not achieve adequate control of chronic pain with monotherapy [5]. Therefore, combination therapy is commonly used in clinical practice, as the association of drugs with different mechanisms of action might improve clinical outcomes [6, 7], even if the use of this therapeutic strategy has been debated [8]. Previous preclinical and clinical

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evidence from randomized controlled trials has suggested the efficacy of combination therapy based on opioid analgesics and calcium channel modulators, since the mechanisms of action of these drug classes are more than additive [2, 9, 10]. However, further investigation is advocated to provide deeper insights into the potential use of this combination therapy in clinical practice.

On this basis, our group is evaluating the efficacy and the effectiveness of combination therapy based on pregabalin, and controlled-release (CR) oxycodone, a strong opioid. CR oxycodone provides a sustained analgesic effect, as suggested in some clinical studies [11–16], and may improve the management of chronic pain that requires continuous treatment [17, 18]. It must be pointed out, however, that the possibility of the onset of tolerance and addiction to this drug is still being debated [19]. Further clinical long-term experimental and observational studies are still needed to shed additional light on the clinical pharmacology of CR oxycodone [17, 18].

Our group has previously conducted a randomized study comparing the effects of combination therapy with CR oxycodone + pregabalin versus both agents as monotherapy in patients with non-cancer pain, which suggested that the combination of CR oxycodone + pregabalin may represent a valuable addition to existing pharmacotherapy for non-cancer pain [2]. Although this study had a randomized design and therefore provided well-grounded evidence, it only evaluated short-term (90-day) use of this combination therapy.

The aim of the present observational study was to evaluate, in a real-life setting, the long-term efficacy and safety of combination therapy with CR oxycodone + pregabalin in a large number of patients who were experiencing chronic non-cancer pain.

Patients and Methods

Study Setting and Design

This prospective cohort study was conducted at Tor Vergata University Hospital, in the Department of Pain Therapy, from July 2008 to January 2010. All patients provided written informed consent before the inclusion in the study. The study was conducted in accordance with the Helsinki Declaration and the Local Ethical Committee approved the study design.

Eligibility Criteria

Consecutive patients aged ≥18 years requiring medical attention at our Center were eligible in this study if they were experiencing chronic pain of non-cancer etiology (score >5 on an 11-point numerical rating scale (NRS), where 0 = no pain; 10 = worst pain imaginable) for ≥6 months. All eligible patients had failed to respond to a variety of analgesic treatments, including opioids and multiple-drug therapy.

Study Treatments and Evaluations

All patients received a combination of oral CR oxycodone (OxyContin®; Mundipharma, Italy) and oral pregabalin (Lyrica®; Pfizer, Italy) for a total period of 1 year. The two drugs were administered according to the manufacturers' prescribing information. Patients were started on dosages included in the ranges recommended by international guidelines [3, 4], as required by their condition and according to the severity of experienced pain. Daily doses of treatment were titrated at scheduled visits at months 1, 2, 4, 6, 9 and 12, in order to achieve optimal efficacy and tolerability on the basis of patient response. Patients were also allowed to refer to the Center at any time during the study period, if necessary. Patients were allowed to continue their current treatment for comorbid diseases. Concomitant analgesic medication (oral morphine 5 or 10 mg/day) was used for the management of breakthrough pain, as required.

At all visits, performed by trained clinicians, patients were asked to rate their pain during the past 24 h according to an 11-point NRS. The drug doses could be modified according to the reported pain intensity as follows: (a) score on NRS = 0, the dose of CR oxycodone was reduced by 20%, and the dose of pregabalin was reduced by 5% at the following visit if the NRS score was still zero; patients reporting an NRS score = 0 for two consecutive visits were withdrawn from the study; (b) reduced or unaltered score on NRS, the doses of both CR oxycodone and pregabalin were not modified; (c) increased score on NRS, the dose of oxycodone was increased by 10% (increase of 1 point on NRS) or by 20% (increase of ≥2 points on NRS).

Adverse events were recorded at each follow-up visit. Patients who did not attend planned visits were considered lost to follow-up. Subjects who withdrew from the study, or lost to follow-up, were contacted by two telephone interviews (1 week after study withdrawal and 1 month after the first interview) to evaluate the possible onset of adverse events and to monitor the onset of addiction; addictions were also monitored by checking drug prescriptions.

Data Analysis

NRS scores at each visit, the subsequent variations in the doses of CR oxycodone and pregabalin, as well as the incidence of adverse events, were analyzed using descriptive statistics. The proportion of patients achieving complete pain relief, and those who required withdrawal from the study for the onset of adverse events, were also evaluated. Differences between time points were evaluated by Student's t test or χ^2 test, as appropriate. $p < 0.05$ was considered statistically significant.

Results

Patient Characteristics

In total, 1,015 patients were enrolled (375 males; mean age 64 ± 15 years, range 21–94 years). Patient demographics and baseline characteristics are summarized in table 1. Radiculopathy (45.9%) represented the most common underlying cause of chronic non-cancer pain, fol-

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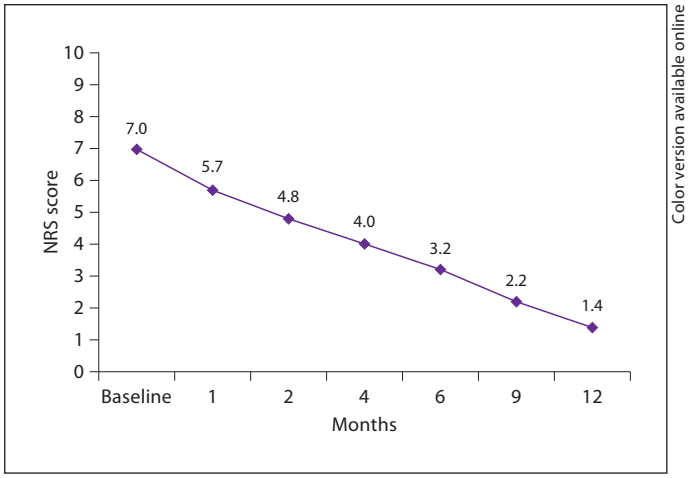

Fig. 1. NRS score during the study period. $p < 0.001$ for all comparisons between consecutive visits.

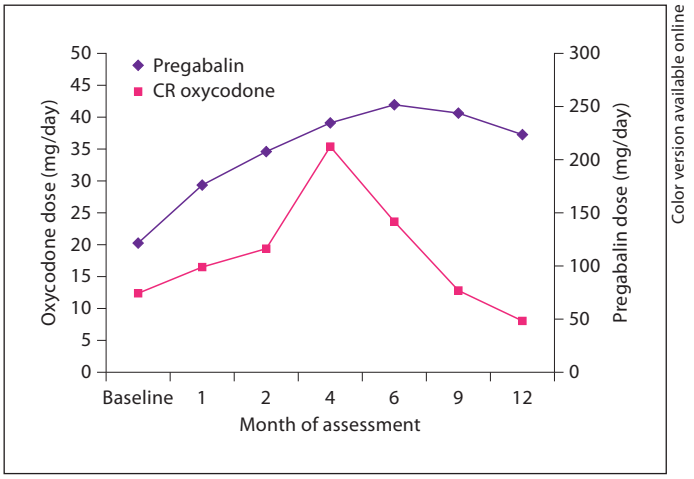

Fig. 2. Mean doses of CR oxycodone and pregabalin at different visits during the observation period. All variations between consecutive visits in oxycodone dose are statistically significant ($p < 0.01$), whereas differences in pregabalin dose reach statistical significance, when compared to previous visit, at 2 and 12 months ($p < 0.01$).

Table 1. Patients' (n = 1,015) demographics and baseline characteristics

Males, n (%)	375 (36.9)
Age, years	
Mean ± SD	64 ± 15
Range	21 – 94
Underlying disease, n (%)	
Radiculopathy	466 (45.9)
Failed back surgery syndrome	177 (17.4)
Postherpetic neuralgia	163 (16.0)
Diabetic neuropathy	114 (11.2)
Other	30 (2.9)
Trigeminal neuralgia	29 (2.8)
Lesion of brachial plexus	12 (1.2)
Post-traumatic diabetic neuropathy	11 (1.1)
Post-actinic diabetic neuropathy	8 (0.9)
Post-infectious diabetic neuropathy	5 (0.5)
NRS score	
Mean ± SD	7.02 ± 1.26
Range	4 – 10

lowed by failed back surgery syndrome and postherpetic neuralgia. Taken together, these conditions affected about 80% of patients. The mean baseline NRS score was 7.02 ± 1.26 (range 4–10). Three patients, all of whom were >65 years old and were affected by severe diseases, died during the study (2 patients from heart failure, diagnosed before the inclusion in the study, and 1 from brain ischemia).

NRS Scores and Mean Doses of Study Drug

The NRS score significantly decreased throughout the 1-year study period (baseline: 7.02 ± 1.26; 12 months: 1.45 ± 0.92; $p = 0.00001$). The reduction in NRS score was >15% between all pairs of consecutive time points ($p < 0.001$ for all comparisons) (fig. 1).

The mean starting dose of CR oxycodone was 12.5 ± 8.4 mg/day (range 10–100), whereas that of pregabalin was 121.7 ± 97.2 mg/day (range 50–600). After an initial increase, the doses of both drugs gradually reduced during the study period (fig. 2): this trend was particularly evident for CR oxycodone (table 2). The significant increase in the dose of CR oxycodone reported at 4 months ($p < 0.01$ vs. 2 months) was associated with a limited number of patients who withdrew from the study due to the onset of adverse events (see next paragraph).

Withdrawals from the Study

A total of 234 patients (23.0% of the total number of participants) withdrew from the study. Of these, 159 (67.9% of withdrawn subjects) withdrew due to the onset of adverse events, and 29 (12.4%) were lost to follow-up (table 3). Of note, 46 (19.7%) patients were withdrawn from the study due to complete relief from chronic pain, with the majority (37 patients) achieving complete pain relief at 4 months.

In most (51.4%) cases, withdrawals from the study were observed at 1 month after inclusion into the study

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Table 2. Percentage variation in the doses of oxycodone and pregabalin at different visits, compared with the previous visit

	1 month	2 months	4 months	6 months	9 months	12 months
Oxycodone	+43.8	+12.8	+60.1	–27.2	–43.5	–29.7
Pregabalin	+44.6	+18.6	+12.4	+7.4	–2.9	–7.4

Table 3. Withdrawals (n = 234) from the study at different time points due to the onset of adverse events, achieving complete pain relief, or lost to follow-up

Reason	1 month	2 months	4 months	6 months	9 months	12 months	Total
Adverse events	83 (35.5)	42 (17.9)	22 (9.4)	10 (4.3)	2 (0.8)	0	159 (67.9)
Complete pain relief	0	13 (5.5)	24 (10.2)	7 (3.0)	2 (0.8)	0	46 (19.7)
Lost to follow-up	1 (0.4)	3 (1.3)	2 (0.8)	10 (4.3)	8 (3.4)	5 (2.1)	29 (12.4)
Total	84 (35.9)	58 (24.7)*	48 (20.6)	27 (11.5)	12 (5.2)	5 (2.1)	234 (100)

All values are expressed as number of patients (%). * p = 0.033 vs. 1 month.

Table 4. Adverse events leading to treatment withdrawal (n = 159)

Adverse event	Patients, n (%)
Constipation	35 (22.0)
Somnolence	24 (15.1)
Nausea	22 (13.8)
Dizziness	19 (11.9)
Vomiting	14 (8.8)
Mental confusion	12 (7.5)
Edema	12 (7.5)
Mood alterations	7 (4.4)
Cephalea	6 (3.8)
Sexual dysfunction	3 (1.9)
Itching	3 (1.9)
Skin eruptions	2 (1.3)

(table 3). At 2 months, the rate of withdrawal was significantly lower than that reported after 1 month (p = 0.033); the trend toward a progressive reduction in the number of withdrawals was consistent throughout the entire study period, even if other significant differences between consecutive time points were not disclosed.

Safety Analysis and Onset of Addiction

The majority of adverse events were of mild-to-moderate severity. A trend towards a decrease in the frequency of adverse events was observed throughout the entire study period ($p < 0.05$ for all comparisons between consecutive visits), with the exception of constipation. Figure 3 reports the number of patients who experienced some selected adverse events (selected based on their potential association with study medication) at different visits.

The most frequent adverse event which resulted in withdrawal from treatment was constipation (22.0% of treatment withdrawals for adverse events), followed by somnolence (15.1%) and nausea (13.8%) (table 4). Vomiting was the cause of withdrawal in 8.8% of discontinuations from the study.

During the planned phone interview, patients reported an absence of persisting pain and adverse events; no cases of addiction were identified.

Discussion

Overall, the results of this long-term and large observational study suggest the feasibility of a combination of CR oxycodone and pregabalin in the treatment of non-cancer pain. To our knowledge, this is the first study to evaluate this combination strategy over a 1-year timeframe.

In particular, a constant and significant decrease in the NRS score was observed throughout the entire study. At all visits, pain was decreased by more >15% with respect to the previous assessment; at the end of the study,

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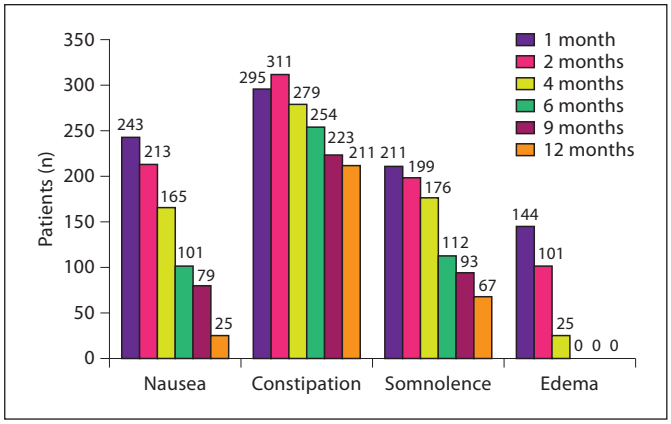

Fig. 3. Number of patients experiencing mild to moderate adverse events (selected according to their potential association with study treatment), at different visits. All comparisons between consecutive visits were statistically significant ($p < 0.05$) for all events, with the exception of constipation (whole study) and edema (last three visits).

the mean NRS score was about 1.5, thus suggesting clinically meaningful relief from chronic pain [2]. However, it must be observed that the proportion of patients achieving complete pain relief, i.e. absence of pain for two consecutive visits, was only 4.5%, likely due to the severity of pain experienced at baseline (mean NRS score = 7).

Of note, the decrease in pain severity was associated, during the first part of the study, with an increase in the dosage of both drugs, which was then followed by a more marked and sustained reduction in the doses administered. At the end of the study, patients were administered a lower dose of oxycodone with respect to baseline. This finding may support the possible existence of an adaptation to opioid therapy, which has been established for patients suffering from cancer pain [20] and is now being suggested for those experiencing non-cancer pain [21].

Overall, the above findings are in line with previous experience conducted by our group [2]. In this randomized study, the combination of CR oxycodone + pregabalin resulted in the largest decrease in NRS score, when compared with CR oxycodone or pregabalin monotherapy (reductions in NRS score: 80, 76, and 46%, respectively). Patients receiving combination therapy also had a more marked increase in quality of life. Combination therapy also allowed a dose reduction of both agents (22% for CR oxycodone and 51% for pregabalin). In another randomized study, which evaluated the combination of extended-release oxycodone and the other Ca^{2+} channel blocker, gabapentin, in the treatment of neuropathic pain, patients on combination therapy experienced a greater reduction in pain score than those receiving gabapentin monotherapy and an improvement in quality of sleep [22]. Combination therapy also determined a lower incidence of discontinuation from treatment due to a lack of efficacy. The present study represents a further extension of the above-described trials, due to its longer follow-up (1 year vs. 90 days for both previous trials).

The tolerability profile and the possibility of the onset of addiction represent a great concern in therapies based upon the administration of an opioid-based therapy, particularly over the long term. Our results suggest an overall favorable tolerability profile for the combination therapy, in line with our previous experience [2]. A relatively high proportion of patients (around 15%) discontinued treatment due to the onset of adverse events, an incidence rate that is comparable to that reported from the study evaluating extended-release oxycodone and gabapentin [22] and higher than that reported in our previous trial [2]. However, the majority of discontinuations were reported at the first visit, 1 month after treatment initiation. This finding, together with the decreasing incidence of some adverse events potentially related to study drugs over time, may suggest that the main concerns about tolerability could be limited to the first period of CR oxycodone + pregabalin therapy. We speculate that this finding might lend further support to a progressive adaptation to opioid therapy over time.

Of note, no episodes of addiction were reported in the present study. The low rate of addiction in patients with chronic pain of non-malignant origin treated with opioids was previously suggested by a systematic review of 67 trials, which reported that the frequency of addiction to opioid therapy is about 3% in patients with chronic pain, even if around 10% of subjects may have aberrant drug-related behaviors [23]. The potential onset of addiction represents a major concern in the current debate on opioid therapy. Further research on this issue is therefore advocated [19, 24]. We believe that a deeper knowledge of opioid use, including their advantages and drawbacks, may allow for more adequate management of patients with chronic non-cancer pain [25].

It must be acknowledged that this observational study has several limitations. The retrospective design and monocentric nature should be considered when interpreting the key findings. Moreover, the lack of an active control group cannot allow a direct comparison with other strategies used for the management of chronic non-cancer pain, and the lack of a placebo control does not allow one to completely rule out the possibility of spontaneous recovery in

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some patients. Data on quality of life were not collected in this present study, potentially limiting the completeness of the results. However, the long-term follow-up of this study and the large population represent strong points which may overcome, at least partially, the inherent limitations due to the study design. It must also be noted that current medical research is emphasizing the importance of observational studies, which may provide clinically meaningful data on long-term effectiveness and safety [26].

In conclusion, this study provides new information, in a real-life scenario, on the efficacy and tolerability of the combination of CR oxycodone and pregabalin over the long term for the treatment of non-cancer pain. This combination therapy was associated with a clinically significant reduction in pain severity, without significant tolerability concerns and no onset of addiction. Based on these results, this combination treatment could represent a valuable therapeutic option.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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